Reye syndrome—insights on causation and prognosis

Reye syndrome (RS) is an abrupt insult to mitochondria manifesting as acute encephalopathy, selective hepatic dysfunction, and fatty infiltration of the viscera—as originally described in 1963 (see Wood). Causation, however, remains unclear, especially the role of aspirin in possible pathogenesis. Although prompt recognition and intensive therapy is essential to full recovery, a paucity of cases in recent years has meant that few younger paediatricians have any personal experience. This and a spate of recent literature—clinical and scientific—has prompted this review.

Background
RS is a biphasic illness. A viral prodrome—with infection of the upper respiratory tract or bowel, or varicella—is followed several days later by an abrupt onset of encephalopathy heralded as profuse, effortless vomiting. The rate and degree of neurological decline vary. Raised intracranial pressure from brain swelling is usually thought to cause death or neurological injury.

The British Paediatric Surveillance Unit defines RS as an unexplained, non-inflammatory encephalopathy in those less than 16 years of age, associated with a serum alanine or aspartate aminotransferases, or plasma ammonia increase and panlobular in distribution. Diagnostic criteria are non-specific. One group maintains that antiemetics taken after the onset of the vomiting have a causal role in RS, another disputes its actual existence; evidence in support of these views is unconvincing and they have gained little support. However, a proportion of those thought initially to have RS (12%) are shown later to have an inherited metabolic disorder (IMD), such as single enzyme defects of the tricarboxylic acid cycle, or the urea cycle. “Classical” RS must of necessity be a diagnosis of exclusion.

Aspirin—a co-factor?
The evidence on prodromal aspirin and RS has been reviewed. Several case-control studies assert that the association is strong, consistent, and unbiased; this is especially true of the very rigorous “Yale” study, in which a dose response effect was also noted. Even a total dose less than 45 mg/kg increased the risk of RS by 25-fold—the authors concluding that “no safe dose of aspirin exists”. No other exogenous agent has been implicated in similar well designed studies (see Hall).

Longitudinal surveillance provides further evidence. A recent review of 1207 cases reported to the National RS Surveillance System (NRSSS) at the Centers for Disease Control and Prevention, Atlanta, USA (1 December 1980 to 30 November 1997) identified 555 cases in 1980, but only two annually between 1994 and 1997; case reporting was to the 18th birthday. In the UK, the annual incidence declined from 81 cases in 1983–84 to five in 1996–97. One elegant study showed that this decline mirrored the upsurge in publications mentioning the link with aspirin that began in the USA in 1980. Furthermore, in Northern Ireland, febrile children admitted to hospital in 1988–89 showed a 17-fold reduction in preadmission aspirin use compared to those in 1985–86 (the Committee on Safety of Medicines warned of the aspirin risk in mid-1986).

Finally, more than 400 UK cases reported between 1982 and 1990 were reviewed “blindly” using a Reye score (devised by Dr Susan Hall to quantitate features characteristic of “classical” RS) employed here in modified form. Highest scores were achieved by a distinct aspirin related subgroup that diminished significantly in number (79%) after 1986. The evidence of an association therefore seems epidemiologically sound, and the disappearance of RS consequent on the aspirin warnings was described two years ago in an editorial in the New England Journal of Medicine as “a public health triumph”.

Aspirin metabolism
Following absorption, aspirin is metabolised rapidly to salicylate. At usual anti-inflammatory doses, with plasma concentrations of 1–5 mM, the half life approximates to 12 hours; at high therapeutic doses it may reach 30 hours. Salicylate is metabolised within hepatocyte mitochondria and endoplasmic reticulum to significant amounts of hydroxyhippurate (HHA) and gentisate. Among 56 patients with RS in Northern Ireland (1979–86), the serum salicylate range and mean on admission were 0–2.5 and 0.9 mM/l, respectively (JG, unpublished data). This concurs with published data; HHA concentrations tend to be twofold higher. In RS, therefore, aspirin metabolites may persist for some time at millimolar concentrations. Are such concentrations capable of influencing events, however?

Viral infection and the immune response
Antecedent viral infection appears to be a sine qua non for development of RS. Viral RNA frequently diverts host endoplasmic reticulum to biosynthesis of viral protein. A number of virus infections disturb Kupffer cell function and endotoxaemia commonly results, triggering a cascade of cytokines. Endotoxin like activity has been reported in plasma and CSF in RS. Endotoxin provokes release by macrophages of tumour necrosis factor (TNF), a known mediator of metabolic toxicity. In rat hepatocytes, for example, TNF inhibits fatty acid oxidation; influenza B virus produces similar effects in mice. Following sublethal doses of endotoxin, rats have increased concentrations of plasma ammonia and free fatty acids, and develop hepatic fatty infiltration and mitochondrial damage. Immature rodents appear more sensitive to the effects of TNF. Aspirin enhances in vitro release of TNF by mouse macrophages. Finally, aspirin and salicylate at 1–5 mM directly inhibit release of the proinflammatory and antiapoptotic nuclear factor Kβ, allowing target cells to proceed more rapidly down the pathway to cell death. Thus viral infection may influence cellular and subcellular events via immune mediators.

Mitochondrial failure
The clinical findings in RS are compatible with hepatotoxicity caused by mitochondrial failure. Mitochondria provide most of the energy for liver cell function via oxidative phosphorylation fed by the tricarboxylic acid cycle and...
β oxidation of long chain fatty acids (LCFA). Mitochondria are also closely involved in cell death processes such as the mitochondrial permeability transition (MPT). This is the opening of a cyclosporin sensitive pore in the inner membrane of mitochondria leading to swelling, depolarisation, failure of oxidative phosphorylation, and cell death by apoptosis or necrosis. Recently, Lemasters’ group has shown that 0.3 mM salicylate can initiate MPT in isolated liver mitochondria, and, in cultured rat hepatocytes, 0.3–5 mM salicylate enhanced cell killing.

In RS the burden of evidence suggests that mitochondrial failure is the result of inhibition of oxidative phosphorylation and fatty acid β oxidation of LCFA. Microvesicular steatosis is a likely consequence and accumulation of tissue LCFA has recently been shown to initiate apoptosis via increased ceramide in a variety of cell types. Another factor is that toxic acyl-CoA esters initiate apoptosis via increased ceramide in a variety of cell types. Generalised mitochondrial dysfunction may only become apparent much later when maturation deviates from normal, and abilities may be simply less well acquired. Moreover mild impairments, perhaps clinically undetectable in themselves, may exert a cumulative influence on the development of other functions, leading to more significant disabilities. Hence the need for outcome studies during the school years and beyond. Among 56 patients seen between 1979 and 1986 (median age 0.8 years), Meekin and colleagues studied cognitive, emotional, and behavioural sequelae in 18 children who had recovered well enough to attend normal schools. The mean age was then 11.75 years, with each child being compared to the sibling nearest in age. On the basis of formal testing, general intellectual functioning, and verbal, and visuospatial skills were significantly reduced if RS occurred during infancy. A similar profile was evident on the measure of self esteem. Differences for measures of behavioural problems failed to reach significance. Another significant variable was the development of unconsciousness during encephalopathy. Although this was not so closely associated with less good outcomes, it was linked to relative deficits on the scale of cognitive ability; however, only those differences on the Wechsler scale of verbal abilities reached statistical significance.

**Prognosis**

If the neurological phase of RS resolves, visceral function is expected to recover completely within a few days. However, the severity and duration of both metabolic and hydrostatic effects on the nervous system will determine prognosis. Although pathogenesis of the brain swelling is unclear, its results can be all too evident, with elevation of intracranial pressure, and, if more severe, reduction in cerebral perfusion pressure; a cerebral perfusion pressure of 40 mm Hg or less in RS carries a very poor outcome. In the NRSSS, even small biochemical abnormalities appeared to influence mortality. Logistic regression analysis showed that, surprisingly, a blood ammonia little greater than the normal upper limit for older children was significantly associated with a risk of demise (p < 0.01)—the relative risk of death being 3.4 and of neurological complications 4.1.

In our series, more than 70% of the children achieved a good initial outcome (62% in NRSSS). This optimism must be interpreted with caution because in the UK, RS has tended to occur at a very young age (median age 14 months; median age in NRSSS, 6 years). Damage to the developing brain that results in neuropsychological deficits may only become apparent much later when maturation deviates from normal, and abilities may be simply less well acquired. Moreover mild impairments, perhaps clinically undetectable in themselves, may exert a cumulative influence on the development of other functions, leading to more significant disabilities. Hence the need for outcome studies during the school years and beyond. Among 56 patients seen between 1979 and 1986 (median age 0.8 years), Meekin and colleagues studied cognitive, emotional, and behavioural sequelae in 18 children who had recovered well enough to attend normal schools. The mean age was then 11.75 years, with each child being compared to the sibling nearest in age. On the basis of formal testing, general intellectual functioning, and verbal, and visuospatial skills were significantly reduced if RS occurred during infancy. A similar profile was evident on the measure of self esteem. Differences for measures of behavioural problems failed to reach significance. Another significant variable was the development of unconsciousness during encephalopathy. Although this was not so closely associated with less good outcomes, it was linked to relative deficits on the scale of cognitive ability; however, only those differences on the Wechsler scale of verbal abilities reached statistical significance.
Conclusion
Long term follow up in RS may in its way be as important as early recognition and optimum management, as are diagnostic investigations aimed at uncovering an IMD. Inhibition of the MTE-LCHAD enzyme system by salicylate and metabolites, and the differences shown for the first time in human material between control and RS cells, lends biological plausibility to the substantial body of epidemiological evidence linking RS with aspirin use during childhood viral illness. Our view is that current warnings about aspirin use must be maintained—with continued case monitoring—to ensure that this potentially devastating encephalopathy does not reappear and that “the public health triumph” will also be fully realised in the UK.

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